http://www.gpo.gov/fdsys/pkg/FR-2014-11-21/html/2014-26197.htm

Executive Summary

Purpose of This Regulatory Action

This proposed rule clarifies and expands requirements for the submission of clinical trial registration and results information to the ClinicalTrials.gov database, which is operated by the NLM. It implements the provisions of section 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. 282(j)), which were added by FDAAA to improve public access to information about certain clinical trials of FDA-regulated drugs, biological products, and devices and certain pediatric postmarket surveillances of a device. Under section 402(j) of the PHS Act, those responsible for specified clinical trials of FDA-regulated products have been required to submit registration information to ClinicalTrials.gov since December 26, 2007, summary results information for clinical trials of approved products since September 27, 2008, and adverse events information since September 27,

2009. Section 402(j) of the PHS Act requires the Secretary of Health and Human Services (HHS) to use rulemaking to expand the requirements for submission of summary results information, and authorizes the Secretary to use rulemaking to make other changes in the requirements for submission of registration and results information.

This proposed rule does not impose requirements on the design or conduct of clinical trials or on the data that must be collected during clinical trials. Instead it specifies how data that were collected and analyzed in accordance with a clinical trial's protocol are to be submitted to ClinicalTrials.gov. No patient-specific data are required to be submitted by this proposed rule or by the law this proposed rule is intended to implement.

## Summary of the Major Provisions of the Regulatory Action

### Applicable Clinical Trial

This proposed rule specifies which clinical trials of FDA-regulated drugs, biological products, and devices and which pediatric postmarket

surveillances of a device, are applicable clinical trials for which information must be submitted to ClinicalTrials.gov. This proposal specifies an approach for determining whether a particular clinical trial or study is an applicable clinical trial, based on descriptive information that would be submitted at the time of registration.

Responsible Party

This proposed rule specifies that there must be one (and only one) responsible party for submitting information about an applicable clinical trial. The sponsor of an applicable clinical trial would be considered the responsible party, unless and until the sponsor designates a qualified principal investigator as the responsible party. This proposed rule specifies the approach for determining who would be considered the sponsor of an applicable clinical trial under various conditions, what qualifies a principal investigator to be designated a responsible party by a sponsor, and how responsibility reverts to the sponsor if a designated principal investigator is unable to fulfill the

requirement to

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submit information to ClinicalTrials.gov.

Registration

This proposed rule specifies requirements for registering applicable clinical trials at ClinicalTrials.gov. It would require that the responsible party register an applicable clinical trial not later than 21 days after enrolling the first participant, and it specifies the data elements of clinical trial information that must be submitted at the time of registration. The proposed data elements include the descriptive information, recruitment information, location and contact information, and administrative data elements listed in section 402(j) of the PHS Act, as well as additional data elements that are proposed under the Secretary's authority to modify the requirements for clinical

trial information due at registration as long as such modifications improve, and do not reduce, the clinical trial information available to the public in ClinicalTrials.gov. We consider the proposed additional data elements necessary to enable the Agency to implement other statutory provisions, indicate the status of human subjects protection review of the trial, facilitate the public's ability to search and retrieve information from ClinicalTrials.gov, and help ensure that entries are unambiguous. Some of these additional data elements were included in ClinicalTrials.gov before FDAAA was enacted.

Expanded Access Information

Section 402(j) of the PHS Act requires the submission of information on how to obtain expanded access to investigational drugs used in applicable clinical trials, if the drugs are available through expanded access programs to patients who are not participating in relevant clinical trials. For an applicable clinical trial of a drug that is available under expanded access, this proposed rule would

require the submission of a separate expanded access record containing details about how to obtain access to the investigational drug. If an expanded access record has already been submitted in conjunction with a different clinical trial of that same drug, the responsible party for the new clinical trial could link to the existing expanded access record rather than create a new one.

Results Submission

This proposed rule implements the statutory requirement for the submission of summary results information for applicable clinical trials of drugs, biological products, and devices that are approved, licensed, or cleared by FDA. It also proposes to extend the requirement for results submission to applicable clinical trials of drugs, biological products, and devices that are not approved, licensed, or cleared by FDA. This proposed rule would require the submission of tables of data summarizing demographics and baseline characteristics of the enrolled participants and primary and secondary outcomes, including

results of any scientifically appropriate statistical tests.

In general, this proposed rule would require the submission of results not later than 1 year after the completion date of the clinical trial, which is defined as the date of final data collection for the primary outcome measure studied. Results submission could be delayed for up to 2 additional years with certification that either an unapproved, unlicensed, or uncleared product studied in the trial is still under development by the manufacturer or that approval will be sought for a new use of an approved, licensed, or cleared product that is being studied in the trial. This proposed rule also permits responsible parties to request extensions to the results submission deadlines for ``good cause''.

Adverse Events

This proposed rule would require the responsible party to submit information summarizing the number and frequency of adverse events experienced by participants enrolled in a clinical trial, by arm and

organ system. It would require submission of two tables of information: one summarizing all serious adverse events; and another summarizing other adverse events that occurred with a frequency of 5 percent or more in any arm of the clinical trial, regardless of whether such adverse events were anticipated or unanticipated.

Updates and Other Required Information

This proposed rule would require that all submitted information must be updated at least annually if there are changes to report. More rapid updating would be required for several data elements to help ensure that users of ClinicalTrials.gov have access to accurate, up-to-date information about important aspects of a clinical trial. This proposed rule also requires timely corrections to any errors discovered by the responsible party or the Agency during review of submissions.

Costs and Benefits

Based on our cost estimates, this regulatory action is not expected to have a significant impact on the economy. The costs consist primarily of the time needed to organize, format, and submit to ClinicalTrials.gov information that was prepared for or collected during the clinical trial (e.g., protocol information and clinical trial results). The benefits include greater public access to information about and evidence from applicable clinical trials (and other clinical trials) of FDA-regulated drugs, biological products, and devices, and greater clarity about what is required for those who are subject to the legal mandate to submit information to ClinicalTrials.gov.

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The calculations below present our estimates of the time and cost associated with meeting the information submission requirements of this proposed rule, including the burden associated with assembling the required information, formatting the information for submission, submitting it to the data bank, and correcting or updating it over time. The calculations break out the estimated annual costs associated

with: (1) registering a trial, (2) submitting results information (including adverse event information), (3) submitting certifications, extension requests and appeals to delay the results submission deadline, (4) submitting clinical trial information that is triggered by a voluntary submission; and (5) creating expanded access records for drugs studied in an applicable clinical trial. The estimates include the costs associated with updating submitted information and with correcting errors detected by NIH. We estimate the total annual cost to be $49,713,753. As explained below, we expect that during the first year after the effective date of this proposed rule, responsible parties will incur some additional time and cost to update clinical trial information that previously was submitted to the data bank for trials that were initiated prior to the effective date and ongoing as of that date. We estimate this additional, non-recurring cost to be $2,457,080.

We expect that over time the cost of complying with this proposed rule will decline notably once a final rule is published and responsible parties become more familiar with the registration and

results submission requirements as well as the data submission and review processes. Many data providers have developed standard operating procedures for data entry personnel and refined their data management systems to facilitate data submission. A number of clinical trial data management software tools currently allow users to output registration information for automatic uploading of files in bulk to ClinicalTrials.gov. We expect that once the requirements for submission of clinical trial information are clarified, responsible parties will automate portions of the data extraction and formatting processes for required results information, significantly reducing the burden of compliance with this proposed rule.

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| Costs prior to rulemaking | $17, 639, 869 |
| Annual costs under proposed rule | $49, 713, 753 |
| Incremental cost above pre-rule | $32, 073,884 |

Table 3--Estimated Burden for Registration and Results Submission at ClinicalTrials.gov

| Type of respondents | Number of respondents | Frequency of response | Average time per response (hours) | Annual hour burden |
|---|---|---|---|---|
| Regulated submissions [Subject to this proposed rule]: | | | | |
| Registration | 7,400 | 1 Initial | 8 | 59,200 |
| | | 8 Subsequent Updates | 2 | 118,400 |
| Results Information | 7,400 | 1 Initial | 40 | 296,000 |
| | | 2 Subsequent Updates | 10 | 148,000 |
| Certifications to delay results | 5,150 | 1 | 0.5 | 2,575 |

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| | | | | |
|---|---|---|---|---|
| Extension requests and appeals | 250 | 1 | 2 | 500 |
| Registration triggered by voluntary submission. | 72 | 1 | 8 | 576 |
| Results triggered by voluntary submission. | 24 | 1 | 45 | 1,080 |
| Expanded access records | 78 | 1 | 2 | 156 |
| SUBTOTAL | ..... | ..... | ..... | 626,487 |
| Non-regulated submissions [Not | | | | |

| | | | | | |
|---|---|---|---|---|---|
| subject to this Proposed Rule]: | | | | | |
| Registration | 9,600 | 1 | Initial | 8 | 76,800 |
| | | 8 | Subsequent Updates | 2 | 153,600 |
| Results Information | 350 | 1 | Initial | 40 | 14,000 |
| | | 2 | Subsequent Updates | 10 | 7,000 |
| SUBTOTAL | | | | | 251,400 |
| TOTAL | | | | | 877,887 |